In the Specification:

Marked copies of the specification revisions have been provided in the attached Appendix I.

Please replace the paragraph from page 2, line 29, to page 4, line 26, with the following paragraph:

-- Hepatocytes are known to have a great many physiological functions, all of which play a very important function in terms of the metabolism of xenobiotics and/or endogenous substrates such as drugs, food additives, environmental pollutants, industrial chemicals and the like. At the same time, the function of metabolizing xenobiotics and/or endogenous substrates might lead to inducing the inhibition of metabolizing enzymes for xenobiotics and/or endogenous substrates by xenobiotics and/or endogenous substrates, to accelerate the activity of metabolizing enzymes for xenobiotics and/or endogenous substrates, to express cytotoxicity by the metabolism of xenobiotics and/or endogenous substrates, to express genotoxicity by the metabolism of xenobiotics and/or endogenous substrates, to express carcinogenicity by the metabolism of xenobiotics and/or endogenous substrates, to express mutagenicity by the metabolism of xenobiotics and/or endogenous substrates, to express hepatotoxicity by the metabolism of xenobiotics and/or endogenous substrates, and so on. For these reasons, the function of xenobiotics and/or endogenous substrates has been widely studied. It is known that many enzymes are associated with the metabolism of xenobiotics and/or endogenous substrates referred to herein. Examples of such enzymes include UDP-glucuronosyltransferase, sulfotransferase, glutathione transferase, epoxy hydratase, N-acetyltransferase, flavin monooxygenase and cytochromes P450. Also, the presence of a cytochrome P450 reductase is crucial for expressing the enzymatic function of cytochromes P450. Of an array of these enzymes, cytochromes P450 play the most important role in the metabolism of xenobiotics and/or endogenous substrates. The term cytochromes P450 collectively refers to a class of enzymes including a great many molecular species. In the metabolism of xenobiotics and/or endogenous substrates in human liver, ten (10) species of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1

and CYP3A4 are considered important. Also, these enzymes, which are distributed in human liver, are functionally different depending on species and hence, human-derived liver specimens are unable to be used as a stable test system. On the other hand, such a metabolic function of the liver involves a very strong specificity, i.e., differences in nature, depending on species, which makes it difficult to predict such diverse metabolic functions of human liver from experimental animals, e.g., rats. However, it is practically impossible to analyze these functions of interest in humans. For these reasons, human-derived cultured hepatocytes are considered useful not only in examining the function of human liver in a rapid, inexpensive, safe and accurate way provided in place of experimental animals, but also in producing a so-called artificial liver as a functional substitute for human liver. However, it is impossible to subculture normal human hepatocytes separated from tissues in vivo. Cells that can be established as a cell line often lack the differentiation capability possessed inherently and in most cases, do not exactly reflect the function of tissues to which the cell line originally belongs. A family of enzymes that metabolize xenobiotics and/or endogenous substrates especially in liver cells, among others, the family of cytochromes P450 molecular species loses its activity in an extremely short period of time in primary culture; any cell line that fully retains the property has not been found so far (J. Dich et al., Hepatology, 8, 39-45 (1988)). Thus, in light of the foregoing, there is an extensive need for hepatocytes that can retain the capability of metabolizing xenobiotics and/or endogenous substrates and can be incubated.--

Please replace the paragraph from page 4, line 27, to page 5, line 10, with the following paragraph:

-- To date, however, no cultured cell line has been obtained as retaining the function associated with the metabolism of xenobiotics and/or endogenous substrates as in the liver. Particularly because the activity of cytochromes P450 is widely recognized to be rapidly lost in cultured cells, it has been hitherto attempted to stably express cytochromes P450 in the established cultured cells and by this, take over the metabolizing function of liver (M. Sawada et al., Mutation Research, 411, 19-43 (1998)). However, as stated above, the cell line for expression of cytochromes P450 should indispensably be derived from human liver cells. In

addition, the activity of NADPH cytochromes P450 reductase is required for expressing the activity of cytochromes P450, requiring further expression of many more enzymes. Therefore, stable and safe reproduction of the metabolizing function in human liver should be in human-derived cultured hepatocytes that retain the activity of enzymes participating in the metabolism of cytochromes P450 as well as various other metabolisms.--

Please replace the paragraph from page 5, line 11, to page 6, line 34, with the following paragraph:

-- As examples of the expression of cytochromes P450 in cells retaining the activity of various enzymes participating in metabolism, there are cases in which P450 was expressed in HepG2 cells using vaccinia virus (Methods in Enzymology, T. Aoyama et al. in Methods in Enzymology, 260, 85-92, edited by M. R. Waterman, Academic Press, 1991) and in which CYP2E1 was expressed in HepG2 cells (Y. Dai et al., Biochemistry, 32, 6928-6937, 1993). In the former case, careful handling is required, which is an obstacle to practical application. The latter was attempted for CYP2E1 alone but so far has not been attempted for many other species of cytochromes P450 present in the liver. Accordingly, if a cultured cell line that can retain the activity of a family of enzymes participating in the metabolism of xenobiotics and/or endogenous substrates in the liver could be obtained, this would enable a practitioner to (1) analyze an enzyme participating in the metabolism of xenobiotics and/or endogenous substrates, (2) analyze a metabolic pathway of xenobiotics and/or endogenous substrates, (3) analyze a chemical structure of the metabolite of xenobiotics and/or endogenous substrates, (4) prepare the metabolite of xenobiotics and/or endogenous substrates, (5) analyze inhibition of the metabolizing enzyme for xenobiotics and/or endogenous substrates, (6) analyze an accelerated activity of the metabolizing enzyme for xenobiotics and/or endogenous substrates, (7) analyze expression of cytotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (8) analyze expression of genotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (9) analyze expression of carcinogenicity by the metabolism of xenobiotics and/or endogenous substrates, (10) analyze mutagenicity by the metabolism of xenobiotics and/or endogenous substrates, (11) analyze expression of hepatotoxicity by the metabolism of xenobiotics and/or endogenous substrates, and (12) analyze xenobiotics and/or

endogenous substrates that act on the liver. Furthermore, this would enable a practitioner to (1) screen a substance capable of inhibiting xenobiotics and/or endogenous substrates, (2) screen a substance capable of accelerating the activity of metabolizing enzymes for xenobiotics and/or endogenous substrates, (3) screen a substance capable of expressing cytotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (4) screen a substance capable of expressing genotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (5) screen a substance capable of expressing carcinogenicity by the metabolism of xenobiotics and/or endogenous substrates, (6) screen a substance capable of expressing mutagenicity by the metabolism of xenobiotics and/or endogenous substrates, (7) screen a substance capable of expressing hepatotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (8) screen xenobiotics and/or endogenous substrates which act on the liver, and (9) screen a substance capable of acquiring a new physiological activity or increasing or decreasing the inherent physiological activity, through the metabolism of xenobiotics and/or endogenous substrates. Thus, specific compounds or salts thereof, etc. can be obtained using the method for analysis and/or the method for screening above.--

Please replace the paragraph from page 7, line 8, to page 8, line 17, with the following paragraph:

-- These cells enable a practitioner of the invention to (1) analyze an enzyme participating in the metabolism of xenobiotics and/or endogenous substrates, (2) analyze a metabolic pathway of xenobiotics and/or endogenous substrates, (3) analyze a chemical structure of the metabolite of xenobiotics and/or endogenous substrates, (4) prepare the metabolite of xenobiotics and/or endogenous substrates, (5) analyze inhibition of the metabolizing enzyme for xenobiotics and/or endogenous substrates, (6) analyze an accelerated activity of the metabolizing enzyme for xenobiotics and/or endogenous substrates, (7) analyze expression of cytotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (8) analyze expression of genotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (9) analyze expression of carcinogenicity by the metabolism of xenobiotics and/or endogenous substrates, (10) analyze mutagenicity by the metabolism of xenobiotics and/or endogenous substrates, (11) analyze the expression of hepatotoxicity by the metabolism of

xenobiotics and/or endogenous substrates, and (12) analyze xenobiotics and/or endogenous substrates that act on the liver. The cells further enable a practitioner of the invention to (1) screen a substance capable of inhibiting xenobiotics and/or endogenous substrates, (2) screen a substance capable of accelerating the activity of metabolizing enzymes for xenobiotics and/or endogenous substrates, (3) screen a substance capable of expressing cytotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (4) screen a substance capable of expressing genotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (5) screen a substance capable of expressing carcinogenicity by the metabolism of xenobiotics and/or endogenous substrates, (6) screen a substance capable of expressing mutagenicity by the metabolism of xenobiotics and/or endogenous substrates, (7) screen a substance capable of expressing hepatotoxicity by the metabolism of xenobiotics and/or endogenous substrates, (8) screen xenobiotics and/or endogenous substrates which act on the liver, and (9) screen a substance capable of acquiring a new physiological activity or increasing or decreasing the inherent physiological activity, through the metabolism of xenobiotics and/or endogenous substrates. Thus, particular compounds or salts thereof, etc. can be obtained, using the method for analysis and/or the method for screening.--

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Please replace the paragraph at page 8, lines 18-25, with the following paragraph:

-- In view of the foregoing problems, the present inventors have made extensive studies. As a result, they have established stable transformants capable of stably expressing cytochromes P450 in a human hepatocarcinoma-derived (or hepatic carcinoma-derived) cell line with an enhanced activity for participation in the metabolism of xenobiotics and/or endogenous substrates. The following further studies have resulted in accomplishing this invention.--

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Please replace the paragraph at page 13, lines 6-11, with the following paragraph:

-- The human hepatic carcinoma cells used can be collected by separating a human hepatic carcinoma-derived cultured cell line (preferably HepG2) from human hepatic carcinoma. Genes that encode various species of cytochromes P450 separately isolated are stably expressed in the human hepatic carcinoma cells.--

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Please replace the paragraph at page 13, lines 12-30, with the following paragraph:

--In order to stably express DNA fragments encoding cytochromes P450, first, DNA fragments encoding, e.g., individual cytochromes P450 are obtained and placed under control of a foreign promoter for expression. The base sequences of DNA fragments encoding cytochromes P450 are available from public database. Based on the base sequences, a cytochromes P450-encoding DNA fragment can be isolated by publicly known methods including PCR, hybridization screening, etc. The DNA fragment thus obtained is inserted into a vector which produces transformants capable of stably expressing a foreign gene in a cultured mammalian cell, whereby a vector for transformation is produced. The resulting vector is transfected into hepatic carcinoma cells by publicly known methods. Transformants are selected by examining the enzyme activity induced by the expression of cytochromes P450 transformed therein, in order to select excellent clones. In addition, clones obtained can be confirmed with stability of their properties through repeated frozen storage.--

Please replace the paragraph from page 13, line 34, to page 14, line 9, with the following paragraph:

-- The term "stably expressing human cytochromes P450" is used to mean that the expression of human cytochromes P450 is not transient and specifically, the activity of cytochromes P450 is not lost when cells are cultured (subcultured). The cells capable of expressing human cytochromes P450 are preferably cells in which not only cytochromes P450 but also enzymes associated with various aspects of metabolism (specifically, UDP-glucuronosyltransferase, sulfotransferase, glutathione transferase, epoxy hydratase, N-acetyltransferase, flavin monooxygenase, etc.) are capable of functioning.--

Please replace the paragraph at page 15, lines 1-17, with the following paragraph:

--For reproducing the function of the liver by expressing cytochromes P450, the cells should thus be those capable of functioning at least, human-derived UDP-glucuronosyltransferase, sulfotransferase, glutathione transferase, epoxy hydratase, N-acetyltransferase or flavin monooxygenase in the cells. One of such cells is cultured cell

HepG2 originating from human hepatic carcinoma. The HepG2 cell is known to be capable of functioning UDP-glucuronosyltransferase, sulfotransferase, glutathione transferase, epoxy hydratase, N-acetyltransferase, flavin monooxygenase and NADPH P450 reductase function in HepG2 (J. Rueff et al., Mutation Research, 353, 151-176 (1996). In light of the foregoing, the present inventors have succeeded in stably expressing cytochromes P450 in HepG2 in order to reproduce the function of human liver in a rapid, inexpensive, safe and accurate fashion.--

Please replace the paragraph at page 15, lines 18-21, with the following paragraph:

--In particular, preferred embodiments include Hepc/3A4.5, Hepc/2E1.3-8, Hepc/2C9.1, Hepc/2C8.46, Hepc/1A2.9, Hepc/1A1.4, Hepc/2B6.68, Hepc/2D6.39, Hepc/2A6L.9, Hepc/2C19.12, etc.--

Please replace the paragraph from page 16, line 25, to page 17, line 10, with the following paragraph:

-- By analyzing a change in the structure of xenobiotics and/or endogenous substrates through exposure of a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450, enzymes that participate in the metabolism of xenobiotics and/or endogenous substrates can be analyzed (J. L. Napoli et al., Methods in Enzymology, vol. 206, pp. 491-501, Ed. by M. R. Waterman et al., Academic Press, 1991; H. K. Kroemer et al., Methods in Enzymology, vol. 272, pp. 99-108, Ed. by M. R. Waterman et al., Academic Press, 1996). Specific examples include identification of an enzyme participating the metabolism of xenobiotics and/or endogenous substrates by analyzing a change in the structure of xenobiotics and/or endogenous substrates upon exposure of a test specimen to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450. Other specific examples include analysis of the mechanism in an enzymatic reaction by analyzing a change in the structure of xenobiotics and/or endogenous substrates upon exposure of a test specimen of interest to the cell, and analysis of substrate specificity.--

Please replace the paragraph at page 18, lines 11-20, with the following paragraph:

-- By collecting the altered product (the so-called metabolite) from xenobiotics and/or endogenous substrates produced as a result of exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and purifying and isolating the product in an appropriate manner, the metabolite of xenobiotics and/or endogenous substrates can be prepared (J. L. Napoli et al., Methods in Enzymology, vol. 206, pp. 491-501, Ed. by M. R. Waterman et al., Academic Press, 1991).--

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Please replace the paragraph from page 18, line 25, to page 19, line 4, with the following paragraph:

-- By exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450, the inhibition of a metabolizing enzyme for xenobiotics and/or endogenous substrates can be analyzed (J. L. Napoli et al., Methods in Enzymology, vol. 206, pp. 491-501, Ed. by M. R. Waterman et al., Academic Press, 1991). Specifically, the inhibition can be detected by the inhibition of cytochromes P450 enzyme activity, reduction in the amount of protein, decreased mRNA, etc. The detection may be made using publicly known methods, including an assay for enzyme activity corresponding to the respective members of P450, Western blotting corresponding to the respective P450 proteins, Northern hybridization corresponding to various P450 mRNAs, RT-PCR, etc.--

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Please replace the paragraph at page 19, lines 10-25, with the following paragraph:

-- By exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and detecting the increased enzyme activity in the metabolism of xenobiotics and/or endogenous substrates, the increased amount of the enzyme or the increased amount of transcription in gene encoding the enzyme, the accelerated activity of the metabolizing enzyme for xenobiotics and/or endogenous substrates can be analyzed (J. Rueff et al., Mutation Research, 353 (1996) 151-176). Specifically, the accelerated activity can be analyzed by detecting the increased enzyme activity of cytochromes P450, the increased amount of protein or the increased mRNA. The detection

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may be made using publicly known methods, including Western blotting corresponding to the respective P450 proteins, Northern hybridization corresponding to various P450 mRNAs, RT-PCR, etc.--

Please replace the paragraph from page 19, line 30, to page 20, line 8, with the following paragraph:

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-- By exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450, the cytotoxicity caused by the metabolism of xenobiotics and/or endogenous substrates can be analyzed. Specifically, the cytotoxicity can be analyzed by observing a morphological change of the cell caused upon exposure of a test specimen; a change in viable cell count determined by publicly known methods including the MTT assay, Trypan Blue staining, Crystal Blue staining, etc.; leakage of intracellular enzyme such as lactose dehydrogenase; a change in structure of cells in the top layer; a change in intracellular enzyme, etc. (D. Wu, et al., Journal of Biological Chemistry, 271 (1996), 23914-23919).--

Please replace the paragraph at page 20, lines 13-28, with the following paragraph:

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-- By exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and then subjecting the cells to the chromosomal aberration test or the micronucleus test, the genotoxicity caused by the metabolism of xenobiotics and/or endogenous substrates can be analyzed. The genotoxicity can also be analyzed by exposing a test specimen to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and then subjecting the cells to the chromosomal aberration test, to the micronucleus test or to the reverse mutation test. This involves assessment of the test specimen altered by the cells in an appropriate assessment system (J. Rueff et al., Mutation Research, 353 (1996) 151-176; M. E. McManus et al., Methods in Enzymology, vol. 206, pp. 501-508, Ed. by M. R. Waterman et al., Academic Press, 1991).--

Please replace the paragraph from page 20, line 33, to page 21, line 12, with the

following paragraph:

-- By exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and then subjecting the cells to the chromosomal aberration test or to DNA modification, the carcinogenicity caused by the metabolism of xenobiotics and/or endogenous substrates can be analyzed. The carcinogenicity can also be analyzed by exposing a test specimen to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450, followed by assessment of the test specimen altered by the cells in an appropriate system for evaluating carcinogenesis (J. Rueff et al., Mutation Research, 353 (1996) 151-176; K. Kawajiri, et al., Cytochromes, P450, Metabolic and Toxicological Aspects, pp. 77-98, ed. by C. Ioannides, CRC Press (1996)).--

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Please replace the paragraph from page 21, line 35, to page 22, line 11, with the following paragraph:

-- The hepatotoxicity by the metabolism of xenobiotics and/or endogenous substrates can be analyzed by exposing a test specimen, e.g., to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450 and then observing the expression of cytotoxicity. Alternatively, it can be analyzed by exposing a test specimen to the human hepatic carcinoma-derived cultured cell line capable of stably expressing cytochromes P450, administering the test specimen altered by the cells to other liver cells, liver slices or removed liver or to an experimental animal and then observing a change in cell or tissue or an in vivo change caused thereby.--

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Please replace the paragraph at page 35, lines 11-30, with the following paragraph:

--HepG2 was maintained in DMEM (Dulbecco's Modified Eagle's medium) supplemented with 10% FCS (fetal calf serum; Bio Whittaker). HepG2 was inoculated on a 60 mm dish and grown 50-60% confluently in a CO_2 incubator followed by transfection of 2 μg of 1A1/pcDNA3.1(+), 1A2/pcDNA3.1(+), 2A6/pcDNA3.1(+), 2B6/pcDNA3.1(+), 2C8/pcDNA3.1(+), 2C9/pcDNA3.1(+), 2C19/pcDNA3.1(+), 2D6/pcDNA3.1(+), 2E1/pcDNA3.1(+) or 3A4/pcDNA3.1(+) using lipofectamine reagent (GIBCO BRL). After

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incubating in 10% FCS-supplemented DMEM medium for 2 days, the medium was replaced with fresh DMEM medium supplemented with 500 μg/ml G418 (GIBCO BRL) and 10% FCS. The medium was replaced every 3 or 4 days to effect cloning of G418-resistant strains. The resulting G418-resistant strains were maintained in DMEM medium supplemented with 200 μg/ml G418 (GIBCO BRL) and 10% FCS. Each of the G418-resistant strains was assayed for the activity of cytochromes P450 by the method described below. Cell lines showing a high activity were measured and cells that expressed the high activity were selected.--

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Please replace the paragraph at page 36, lines 3-18, with the following paragraph:

--CYP1A1- or CYP1A2-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, ethoxyresorufin previously diluted to 500 μM was added in 500 μl/well. After reacting at 37°C in the dark, the reaction solution was recovered from each well. After 1800 μl of methanol (Wako Junyaku K.K.) was added to 300 μl of the reaction solution and insoluble material was removed by centrifugation, fluorescent intensity was measured at an excited wavelength of 550 nm and a fluorescence wavelength of 586 nm using a spectrofluorometer to quantify the resorufin formed. The product purchased from Molecular Probes was used as the standard substance for resorufin (Molecular Probes).--

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Please replace the paragraph from page 36, line 30, to page 37, line 8, with the following paragraph:

-- CYP2A6-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, coumarin previously diluted to 500 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. The reaction solution was diluted to 10-fold with 0.1M Tris-HCl (pH 7.4) and fluorescent intensity was measured at an excited wavelength of 390 nm and a fluorescence wavelength of 440 nm using a

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spectrofluorometer to quantify 7-hydroxycoumarin formed. The product purchased from Extrasynthese was used as the standard substance for 7-hydroxycoumarin.--

Please replace the paragraph at page 37, lines 19-33, with the following paragraph:

-- CYP2B6-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, 7-ethoxycoumarin previously diluted to 500 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. The reaction solution was diluted to 10-fold with 0.1M Tris-HCl (pH 7.4) and fluorescent intensity was measured at an excited wavelength of 390 nm and a fluorescence wavelength of 440 nm, using a spectrofluorometer (Hitatchi Spectrofluorometer F-2000) to quantify 7-hydroxycoumarin formed. The product purchased from Extrasynthese was used as the standard substance for 7-hydroxycoumarin.--

Please replace the paragraph at page 38, lines 9-20, with the following paragraph:

-- CYP2C8-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, taxol diluted previously to 30 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. After an equal volume of acetonitrile (Wako Junyaku K.K.) was added to and mixed with the reaction solution, insoluble material was removed by centrifugation. 6α-Hydroxypaclitaxel formed in the reaction solution was quantified on HPLC.--

Please replace the paragraph at page 39, lines 6-17, with the following paragraph:

-- CYP2C9-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, tolbutamide previously diluted to 500 μM was added in 500 μl/well. After

reacting at 37°C, the reaction solution was recovered from each well. After an equal volume of acetonitrile (Wako Junyaku K.K.) was added to and mixed with the reaction solution, insoluble material was removed by centrifugation. Hydroxytolbutamide formed in the reaction solution was quantified on HPLC.--

Please replace the paragraph at page 40, lines 4-15, with the following paragraph:

-- CYP2C19-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, mephenytoin previously diluted to 100 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. After an equal volume of acetonitrile (Wako Junyaku K.K.) was added to and mixed with the reaction solution, insoluble material was removed by centrifugation. 4'-Hydroxymephenytoin formed in the reaction solution was quantified on HPLC.--

Please replace the paragraph at page 41, lines 2-10, with the following paragraph:

-- CYP2D6-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, bufralol previously diluted to 200 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well and 1'-hydroxybufralol formed in the reaction solution was quantified on HPLC.--

Please replace the paragraph from page 41, line 34, to page 42, line 11, with the following paragraph:

--2E1-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, p-nitrophenol previously diluted to 500 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. To 100 μl of the reaction solution 50 μl

of NaOH (Wako Junyaku K.K.) was added, and insoluble material was removed by centrifugation. By measuring absorbance at 540 nm - 620 nm, 4-nitrocatechol formed was quantified. 4-Nitrocatechol purchased from Wako Junyaku K.K. was used as the standard substance.--

Please replace the paragraph at page 42, lines 22-33, with the following paragraph:

-- CYP3A4-expressing cells were inoculated on a 12-well plate (Falcon) and incubated in a CO_2 incubator so as to become confluent. After incubation, the medium was suctioned and cells adhering to the plate were washed with Phenol Red-free DMEM medium. Subsequently, testosterone previously diluted to 100 μM was added in 500 μl/well. After reacting at 37°C, the reaction solution was recovered from each well. After an equal volume of acetonitrile (Wako Junyaku K.K.) was added to and mixed with the reaction solution, insoluble material was removed by centrifugation. 6β-Hydroxytestosterone formed in the reaction solution was quantified on HPLC.--

Please replace the paragraph at page 46, line 8, with the following paragraph:

--Results: see FIGS. 1 and 2--

Please replace the paragraph at page 49, line 10, with the following paragraph:

--Results: see FIGS. 4 and 5--

Please replace the paragraph at page 49, lines 12-27, with the following paragraph:

-- It is considered that after cyclophosphamide is hydrolyzed at the 4-position, phosphoramide or acrolein formed by non-enzymatic degradation would act as an alkylating agent to cause hepatic cytotoxicity triggered by covalent binding to macromolecular components in liver cells (K. H. Thomas, et al., Cancer Research, vol. 53, pages 5629-5637, 1993). Cyclophosphamide caused a leakage of LDH in Hepc/2B6.68 cells concentration-dependently in the concentration up to 2 mM and then reached the plateau at the following concentrations. Cyclophosphamide was slightly cytotoxic also in HepG2 (FIG. 4). Turning to the MTT assay method, cyclophosphamide caused a slight decrease of the MTT activity

29 concentration-dependently in Hepc/2B6.68 cells (FIG. 5). Cyclophosphamide was metabolized by the CYP2B6 activity, and the metabolic intermediate formed showed cytotoxicity.--